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Original Article

A gonadotropin releasing hormone agonist trigger of ovulation with aggressive luteal phase support for patients at risk of ovarian hyperstimulation syndrome undergoing controlled ovarian hyperstimulation

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ABSTRACT

Objective: The aim of this study was to determine the efficacy and safety of luteal phase support using human chorionic gonadotropin (hCG) in cycles that are triggered with a gonadotropin-releasing hormone (GnRH) agonist in a moderate-to-high risk population undergoing a GnRH antagonist protocol.
Materials and methods: We retrospectively reviewed the charts of patients undergoing an *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycle with a GnRH antagonist protocol from September 2011 to August 2012. The patients were defined as at high risk for ovarian hyperstimulation syndrome (OHSS) in terms of anti-Müllerian hormone (AMH) and antral follicle counts (AFCs). The patients were divided into two groups depending on whether ovulation was triggered with hCG or a GnRH agonist. Modified luteal support was provided for the cycles triggered by the GnRH agonist via low dose hCG (1500~5000 IU). For the cycles that were triggered by hCG, urinary hCG (5000 IU) following two doses of recombinant hCG (250 μg) were administered. The primary outcomes of this study were the clinical pregnancy rate and the OHSS rate of the two groups. The secondary outcomes were the number of oocytes retrieved and the number of good quality embryos obtained.
Results: The study group and the control group were similar in terms of the primary and secondary outcome measures.
Conclusion: Aggressive luteal support with low dose hCG following a GnRH agonist trigger can result in a comparable pregnancy rate to that with the use of a traditional hCG ovulation trigger. However, OHSS can still occur in patients with risk factors. Therefore, other OHSS prevention strategies should be considered.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is one of the most common iatrogenic side effects of controlled ovarian hyperstimulation. The incidence of the more severe forms of OHSS can reach 3.1–8% [1]. For the primary prevention of OHSS, high-risk patients are identified to individualize ovarian stimulation. The methods of individualization include choosing the proper protocol and minimizing the gonadotropin dose required to achieve adequate oocyte maturation. A meta-analysis found that patients who are treated with a gonadotropin-releasing hormone (GnRH) antagonist have significantly shorter ovarian stimulations, receive lower dose of gonadotropins, and exhibit fewer growing follicles [2]. Consequently, the incidence of severe OHSS is significantly reduced, and the interventions required to prevent OHSS are decreased [2]. In contrast, the pituitary gland remains responsive to GnRH agonists when GnRH antagonists are introduced to prevent a premature luteinizing hormone (LH) surge. Thus, GnRH agonists represent an alternative ovulation trigger in a GnRH antagonist-based protocol.

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In a GnRH antagonist-based cycle, similar numbers of oocytes and embryo qualities are obtained independent of whether the final oocyte maturation is triggered by human chorionic gonadotropin (hCG) or a GnRH agonist. Moreover, GnRH agonists have the advantages of producing follicle-stimulating hormone (FSH) surges that are more similar to the natural cycle and reducing the risk of OHSS [3]. However, cycles triggered with GnRH agonists have been associated with poor clinical outcomes and extremely high early pregnancy loss rates in early randomized control trials [3–5]. According to the current literature, these phenomena seem to be associated with the inadequate luteal support caused by early luteolysis [6]. Therefore, modified luteal support methods, including low dose hCG, recombinant LH, and intensive estrogen and progesterone, have been proposed in some studies [7–11].

In a study conducted by Emperaire et al [12], patients with luteal phase defects in intrauterine insemination (IUI) cycles triggered by a GnRH agonist (triptorelin 0.1 mg) were randomized to different ovulation triggers that primarily varied in terms of triptorelin dose and frequency and the addition of luteal support. Although this study concluded that luteal phase defects might be related to patient characteristics, none of the patients in the group received hCG 12 hours after ovulation triggering for luteal support developed luteal phase defects [12]. Moreover, another study found that patients who received 1500 IU hCG 35 hours after GnRH agonist ovulation triggering exhibited a pregnancy rate comparable to those who received hCG for ovulation triggering [9]. Subsequent randomized studies revealed that low dose hCG for luteal support significantly reduces the occurrence of severe OHSS without compromising pregnancy rate [7,10]. Based on these findings, our study sought to examine the efficacy and safety of protocols involving GnRH agonist ovulation triggers and low dose hCG for luteal support in patients at high risk for OHSS.

Materials and methods

Patient selection

We retrospectively reviewed the charts of patients who underwent *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycles with GnRH antagonist protocols from September 2011 to August 2012. Patients were defined as being at a high risk of OHSS and were included in this study if their antral follicle count (AFC) was ≥15 or their anti-Müllerian hormone (AMH) was ≥3.4 ng/mL according to previous studies [13,14]. Only the first cycle of each patient was included in the study. The only exclusion criterion was a low response following a standard dose of FSH stimulation according to the Bologna criteria (i.e., <3 oocytes retrieved and an E2 level <500 pg/mL on the day of the ovulation trigger) [15].

Protocol design

All patients received daily doses of 150–250 IU of FSH (Gonal-F, Merck Serono, Modugno, Italy or Puregon, N.V. Organon, Oss, The Netherlands) or human menopausal gonadotropin (Menopur, Ferring, Lausanne, Switzerland) for ovarian stimulation according to the physician's experience. Premature LH surges were prevented with 0.25 mg of the GnRH antagonist (Centriotide, Merk Serono) on stimulation Day 5 until the day of ovulation trigger. When at least two leading follicles were >1.6 cm, the ovulation trigger was given. The patients were divided into two groups according to the ovulation trigger employed: 10,000 IU hCG (Pregnyl; N.V. Organon, Oss, Netherlands), or GnRH agonist (Decapeptyl 2.0 mg, Ferring or Luprelide 2.5 mg; Takeda, Osaka, Japan). Oocyte retrieval was performed 34 hours after ovulation trigger. The collected oocytes were inseminated via IVF or ICSI, according to the condition of sperm. The embryos were transferred between Day 2 and Day 5, and the numbers of embryos transferred ranged from one to four.

Nearly all of the patients received micronized progesterone (800 mg, Utrogestan; Besins International Belgique S.A., Drogenbos, Belgium) orally or vaginally and estradiol valerate (4~12 mg, Estrade, Synmosa, Hsinchu, Taiwan) orally daily for 14 days after embryo transfer. In the hCG group, 5000 IU urinary hCG was administered on the day of embryo transfer. Two doses of 250 μg recombinant hCG (Ovidrel, Merk Serono) were given every other day thereafter if no clinical symptoms of OHSS, such as nausea, vomiting, ascites, etc., were observed. Modified luteal support for the cycles triggered by the GnRH agonist was provided with intramuscular injection of progesterone (50 mg) every other day or single dose intramuscular injection of hydroxyprogesterone caproate (125 mg, Progeston depot, Fuji Pharma, Tokyo, Japan) and urinary hCG (1500–5000 IU) every other day until Day 8 following oocyte retrieval. The primary outcomes were the clinical pregnancy rate and the incidence of OHSS of at least moderate severity. The secondary outcomes were the numbers of oocytes retrieved and the numbers of good quality embryos obtained. To further increase similarity of the two groups in terms of OHSS risk, we concurrently analyzed patients with AFCs ≥15 and AMHs ≥3.4 ng/mL.

Diagnosis of OHSS

The diagnosis and severity determination of OHSS were performed according to the grading system developed by Navot et al [16]. Moderate OHSS was defined by the presence of ascites and enlarged ovaries of 8–12 cm. Severe OHSS was defined by the presence of ascites and enlarged ovaries with or without hydrothorax, edema, oliguria, hematocrit levels >45%, WBC counts >15,000/μL, a serum Creatinine (Cr) of 1–1.5 mg/dL, and abnormal results of liver function tests. Early and late onset OHSS were differentiated by the occurrence of symptoms before or after 10 days following the ovulation trigger.

Data analyses

The primary outcomes of this study were the clinical pregnancy rates and the OHSS rates of the two groups. The secondary outcomes were the numbers of oocytes and good quality embryos obtained. The data were processed using the SPSS version 19.0 (IBM, Somers, NY, USA). Analyses of variance and Student *t* tests were used to compare the outcomes between the two groups. A value of $p < 0.05$ was considered significant.

Results

A total of 19 patients were included in the GnRH agonist trigger group, and 63 patients were included in the hCG trigger group from September 2011 to August 2012. In terms of basic backgrounds, the two groups were similar in age, body mass index (BMI), Day 3 FSH, AMH and AFC (Table 1). The clinical outcomes of the two groups are listed in Table 2. After ovulation trigger, the average numbers of oocytes obtained were 15.2/cycle in the GnRH agonist trigger group and 12.2/cycle in the hCG trigger group ($p = 0.84$). The 2 pronuclear stage (2PN) embryo yields were 7.7 in the GnRH agonist trigger group and 6.3 in the hCG trigger group ($p = 0.65$). The average numbers of embryos transferred were 2.84 in the GnRH agonist trigger group and 2.89 in the hCG trigger group ($p = 0.37$). The overall pregnancy rates were 58% in the GnRH agonist trigger group and 52% in the hCG trigger group ($p = 0.32$). Three patients (16%) in the GnRH agonist trigger group and five (8%) in the hCG trigger group developed OHSS ($p = 0.56$). Among these patients, one (5.2

Table 1
Basic data for the patients meeting the inclusion criteria of AFCs ≥15 or AMH levels ≥3.4 ng/mL.

	GnRH agonist ($n = 19$)	hCG group ($n = 63$)	p[a]
Age (y)	33.6 ± 4.9	34.1 ± 3.8	0.08
BMI (kg/m^2)	20.4 ± 2.4	21.3 ± 2.6	0.39
Day 3 FSH (mIU/mL)	6.5 ± 1.9	7.2 ± 2.6	0.70
AMH (ng/mL)	7.5 ± 3.6	6.1 ± 3.3	0.18
AFC	15.7 ± 3.6	12.3 ± 4.3	0.24
FSH dose used (IU)	1543 ± 461	1873 ± 580	0.30
hCG day E2 (pg/mL)	2552 ± 994	1713 ± 937	0.42

Values are expressed as the mean ± standard deviation.
AFC = antral follicle count; AMH = anti-Müllerian hormone; BMI = body mass index; FSH = follicle-stimulatin hormone; hCG = human chorionic gonadotropin; GnRH = gonadotropin-releasing hormone.
[a] Calculated by t test.

Table 2
Clinical results following ovulation trigger for the patients with AFCs ≥15 or AMH levels ≥3.4 ng/mL.

	GnRH agonist ($n = 19$)	hCG group ($n = 63$)	p[b]
Oocytes retrieved[a]	15.2 ± 5.9	12.2 ± 6.3	0.84
MII oocytes[a]	11.3 ± 1.3	8.8 ± 0.7	0.08
2PN[a]	7.7 ± 4.4	6.3 ± 3.6	0.65
No. of embryos transferred[a]	2.8 ± 0.9	2.9 ± 0.8	0.37
Pregnancy rate (%)	58	52	0.32
OHSS rate (%)	16	8	0.06
Severe OHSS (%)	11	6	0.24

hCG = human chorionic gonadotropin; GnRH = gonadotropin-releasing hormone; MII = Metaphase II; 2PN = 2 pronuclear stage embryos; OHSS = ovarian hyperstimulation syndrome.
[a] Values are expressed as mean ± standard deviation.
[b] Calculated by t test.

%) in the GnRH agonist trigger group and one (1.6%) in hCG trigger group exhibited early onset OHSS. Severe OHSS occurred in two cycles of the GnRH agonist trigger group and four cycles of the hCG trigger group (11% vs. 6%, $p = 0.237$).

Twelve out of the 19 patients in the GnRH agonist trigger group and 13 out of the 63 patients exhibited simultaneous AFCs ≥15 and AMHs ≥3.4 ng/mL. Regarding the general data, the women in the GnRH agonist group were older than those in the hCG group (33.8 ± 4.9 years vs. 33.2 ± 3.4 years, $p = 0.04$), but BMI, Day 3 FSH, AMH, AFC, FSH dose used, and hCG day E2 were similar (Table 3). The clinical pregnancy rates of the GnRH agonist and the hCG groups were 50% and 62%, respectively ($p = 0.44$). The OHSS rates were 25% and 23% ($p = 0.83$) in the GnRH agonist and hCG groups, respectively (Table 4).

Table 3
Basic data for the patients who simultaneously met the inclusion criteria of AFC ≥15 and AMH level ≥3.4 ng/mL.

	GnRH agonist ($n = 12$)	hCG group ($n = 13$)	p[a]
Age (y)	33.8 ± 4.9	33.2 ± 3.4	0.04*
BMI	20.8 ± 2.6	21.3 ± 2.3	0.74
Day 3 FSH (mIU/mL)	7.0 ± 1.9	7.0 ± 1.6	0.87
AMH (ng/mL)	7.7 ± 3.6	6.1 ± 2.1	0.15
AFC	15.7 ± 3.0	12.1 ± 2.5	0.99
FSH dose used (IU)	1395 ± 461	1628 ± 343	0.33
hCG Day E2 (pg/mL)	2635 ± 994	1930 ± 810	0.35

Values are expressed as mean ± standard deviation.
AFC = antral follicle count; AMH = anti-Müllerian hormone; BMI = body mass index; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; GnRH = gonadotropin-releasing hormone.
[a] Calculated by t test.

Table 4
Clinical results following ovulation trigger among patients with both AFCs ≥15 and AMH levels ≥3.4 ng/mL.

	GnRH agonist ($n = 12$)	hCG group ($n = 13$)	p[b]
Oocyte retrieved[a]	15.5 ± 6.6	16.2 ± 6.9	0.80
MII oocytes[a]	11.8 ± 1.7	9.8 ± 1.2	0.33
2PN[a]	8.7 ± 4.8	8.1 ± 3.6	0.32
No. of embryos transferred[a]	2.8 ± 0.9	2.8 ± 0.7	0.50
Pregnancy rate (%)	50	62	0.44
OHSS rate (%)	25	23	0.83
Severe OHSS (%)	17	16	0.87

hCG = human chorionic gonadotropin; GnRH = gonadotropin-releasing hormone; MII = Metaphase II; 2PN = 2 pronuclear stage embryos; OHSS = ovarian hyperstimulation syndrome.
[a] Values are expressed as mean ± standard deviation.
[b] Calculated by t test.

Discussion

The risk factors for OHSS include young age, low BMI, polycystic-ovary pictures, high serum E2, multiple stimulated follicles, and high AMH. E2 level had been thought to play a major role in OHSS and had been suggested as an indicator of ovulation induction with GnRH agonists. Lee et al [14] showed that an AMH cut-off value of 3.36 ng/mL provided a sensitivity of 90.5% and a specificity of 81.3% in the OHSS prediction in a prospective study. This study also reported that AMH is a better predictor of OHSS than E2 level. By contrast, Kwee et al [13] showed that a cut off level of >14 antral follicles provided the greatest sensitivity (82%) and specificity (89%) and also the highest accuracy. We included patients with AMHs >3.4 ng/mL or AFC >15 rather than using an E2-based threshold, because the pathogenesis of OHSS relies on some vasoactive factors, particularly vascular endothelial growth factor (VEGF), that are secreted by granulosa cells. Our total OHSS rate was 10.2%, which is greater than the incidence in the general population.

Although the triggering of ovulation with GnRH agonists has the advantages of FSH surges that are more similar to the natural cycle and a lower rate of OHSS, early studies that used GnRH agonists to trigger ovulation reported low pregnancy rates [3,5]. Previous studies of mammalian cycles have shown that the LH surges induced by GnRH agonists are shorter in duration than those induced with hCG, despite repeated GnRH agonist injections [17,18]. Potential reasons for the lower ongoing pregnancy rates following GnRH agonist triggering might be the adverse effects on oocytes, embryos, or detrimental endometrium caused by the shorter duration of the gonadotropin surge and defective corpus lutea [17–19]. In our study, the numbers of metaphase II oocytes yielded were similar between the two groups (GnRH agonist and hCG: 11.3 ± 1.3 vs. 8.8 ± 0.7, respectively, $p = 0.08$). The numbers of 2PN embryos obtained from the two groups were also similar. These findings are compatible with previous evidence that cycles with GnRH agonist ovulation triggers exhibit good oocyte maturation and embryo quality [3,20]. These findings supported the notion that low pregnancy rates of the cycles triggered with the GnRH agonist were not related to adverse effects on the oocytes and embryos. Moreover, good pregnancy outcomes have also been shown in donor–recipient cycles [20]. Detrimental effects on the endometrium due either to direct effects of the GnRH agonist on endometrial receptivity or defective corpus lutea seemed responsible for the poor pregnancy outcome. The alternative proposition is not plausible, because the long protocol used the GnRH agonist to prevent premature LH surges without compromising the pregnancy rate. As mentioned previously, the LH duration was shorter in the GnRH agonist group, and LH function was maintained by hCG for a longer period of time, due to its

biochemical similarity and longer half-life. Early human and animal studies have shown that the withdrawal of LH can cause irreversible luteolysis and further malfunction of the corpus luteum [21,22]. Some studies have reported lower steroid hormone levels and shorter luteal phases when GnRH agonists are used to trigger ovulation [6,10]. The abrupt decrease in steroid hormones also causes endometrial instability and compromises [23]. Despite the lower concentration of estrogen and progesterone in cycles that are triggered with GnRH agonists, the levels are still supraphysiological and suppress LH production. This different steroid pattern combined with the shorter duration of the LH surge, causes the follicles to fail to develop corpus lutea or early luteolysis [10]. For the above reasons, modified luteal support was proposed to rescue the irreversible effect of luteolysis in cycles with GnRH agonist triggers following ovarian stimulation.

Methods for modified luteal support that have been detailed in previous studies include low dose hCG, LH, and intensive estrogen and progesterone [7,8,10,11]. Previous studies have concluded that low dose hCG for luteal support can reduce the occurrence of OHSS without compromising the pregnancy rate. A review conducted by Engmann and Benadiva [19] also reported good clinical and ongoing pregnancy rates with low OHSS rates of 0% in normal responders and 7.7–8.3% in high responders. In our group, we used two doses of recombinant hCG (250 μg) in the hCG triggering group, while urinary hCG (1500 IU to 5000 IU) with intensive estradiol and progesterone were given to the GnRH agonist-triggered group. The OHSS rates were 16% in the GnRH agonist group and 8% in the hCG group when the patients' AMHs were >3.4 ng/mL or their AFCs were >15. There was no statistically significant difference and the occurrence of OHSS in the GnRH agonist group was not decreased compared to the hCG group. This result contrasts with the results of previous studies that have used low dose hCG for luteal support [3,5,7,24]. The reasons for this discrepancy might be that we included high-risk patients, used different criteria, and examined a small number of patients in our study group. One of the most important reasons for this discrepancy might be the overdose of hCG that was used for luteal support. A study published by Castillo et al [7] found that the occurrence of OHSS is associated with the hCG dose used for luteal support [7]. In our data, the occurrence was not related to hCG dose. This finding is possibly related to the fact that the lowest dose of hCG used in our study was above the threshold for decreasing the occurrence of OHSS. The lowest hCG dose that prevents the occurrence of OHSS without compromising pregnancy rate should be established with further study. Another strategy that should be considered is the freezing of all embryos to achieve an hCG-free cycle. One prospective study indicated that GnRH agonist-triggered cycles in combination with freeze-all resulted in a 2% OHSS occurrence rate and 37% cumulative pregnancy rate/patient in the high-risk group [25]. Subsequently, another retrospective study compared fresh transfer and freeze-all followed by one frozen embryo transfer approaches in high-risk patients undergoing GnRH agonist-triggered cycles, and found comparable pregnancy outcomes without occurrence of OHSS [26].

In conclusion, we found that pregnancy rate was not compromised when hCG was used for luteal support in GnRH agonist-triggered cycles. However, the occurrence of OHSS might not be reduced by GnRH agonist triggers when hCG was used for luteal support. These findings indicate that other strategies for the prevention of OHSS should be considered when GnRH agonists are used to trigger ovulation. Further studies might determine the amount of hCG that is required to reduce the OHSS while simultaneously maintaining a comparable pregnancy rate. Additionally, the freezing of all embryos for frozen embryo transfer should be considered.

Conflicts of interest

None declared.

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